REMARKS

Applicants have discovered that dry powder pharmaceutical formulations which include a biologically active polypeptide and an absorption enhancer are an effective and desirable means for achieving systemic delivery of the polypeptide via pulmonary administration. Inclusion of an absorption enhancer was found to improve markedly the systemic absorption of the polypeptide in the lungs.

The dry powder formulation of the invention is designed for inhalation from a "dry powder inhaler," which is a term of art used specifically to refer to a class of inhalers which deliver dry powder pharmaceuticals without the use of a chemical propellant. These inhalers typically utilize the force of the patient's breath to draw the particles of powder into the patient's respiratory system.

Another class of inhalers, termed "powder metered dose inhalers" (or "powder MDIs"), also delivers particles of powder, but supplies them suspended in a liquified propellant (traditionally a chlorofluorocarbon, or CFC) in a pressurized canister. Often a surfactant is included in the powder MDI formulation to help hold the particles in suspension within the liquid propellant. Such powder/propellant formulations are obviously not suitable for inhalation from a dry powder inhaler, and so are not within the invention as claimed.

Claims 1-60 are pending, new claims 33-60 having been added by the above amendment. The amendments to claims 1, 17, and 21 are supported in the specification, e.g., at page 6,

lines 5-7, and at page 10, lines 9-15. The amendments to claim 22 merely clarify the intended scope of the invention. New claims 33-60 derive their limitations from the prior existing claims. No new matter has been introduced.

In the Office Action issued with respect to the parent case on April 24, 1996 (the "Office Action"), claims 1-22 and 26-32 were rejected under 35 USC §102(e) and/or §103 and, for some of the claims, 35 USC §112, ¶2. These rejections were discussed in the in-office interview held on August 22, 1996 (the "interview"), in which participated the Examiner, the Examiner's supervisor, Dr. Kjell Bäckström, Ms. Jenny Vaughan, and the undersigned. In the course of that interview, the Examiner and his supervisor indicated that the arguments presented by Applicants would be likely to overcome all of the rejections. These arguments are set forth below.

Rejection under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 4, 12, and 27 under 35 U.S.C. §112, ¶2, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. This rejection is traversed.

According to the Office Action, claims 4 and 27 are indefinite because they recite an "analogue" of certain specified polypeptides. As discussed in the interview, this term is used in a very limited sense to refer to certain polypeptide species well known in the art. The Examiner and his supervisor agreed in the interview that the evidence submitted by Applicants was

persuasive on this point. A copy of this evidence is attached hereto as Exhibit A.

Similarly, the Examiner and his supervisor agreed that the evidence presented in the interview concerning the terms "bile salt derivative" (see Exhibit B attached hereto) and "cyclodextrin or derivative thereof" (Exhibit C) established that these terms are sufficiently definite to be readily understood by one of ordinary skill in the art.

In view of the above, Applicants request that the rejections under 35 USC §112, ¶2 be withdrawn.

Rejections under 35 U.S.C. §102(e) and §103

A. Platz et al.

The Examiner rejected claims 1-14, 17-22, and 26-29 under 35 U.S.C. §102(e) as anticipated by Platz et al. (U.S. Pat. No. 5,284,656). Alternatively, the claims are said to be obvious under 35 U.S.C. §103 over the same reference.

As discussed in the interview, Platz et al. describe two general types of powder formulations: one which is intended for inhalation from a dry powder inhaler (col. 4, lines 20-29), and one which is intended for inhalation from a powder MDI (col. 4, lines 5-17), i.e., in conjunction with a liquified propellant. Only the latter formulation includes a surfactant. The surfactant included in the powder MDI formulation is specifically included to aid in keeping the powder particles suspended in the propellant (col. 4, lines 8-9). The particular surfactants mentioned by Platz et al. (sorbitan trioleate, soya

lecithin, and oleic acid) are oils or oily waxes at room temperature. As Applicants disclosed on page 10, lines 11-15, of the present application, an enhancer suitable for use in a dry powder inhaler should exhibit "good powder properties, i.e., lack of a sticky or waxy consistency in the solid state." Since the powder MDI formulations described by Platz et al. (a) do not include anything that could be deemed an absorption enhancer that is a "non-waxy solid at room temperature" (the temperature at which a dry powder inhaler would normally be used), and (b) are not "suitable for inhalation from a dry powder inhaler", these two criteria of claim 1, as amended, are not met by Platz et al. Thus, neither Platz et al.'s dry powder inhaler formulation nor their powder MDI formulation is within any of the claims, and the rejection under §102(e) should be withdrawn.

Furthermore, Platz et al. cannot be said to render the present invention obvious. Nothing in Platz et al. suggests including an absorption enhancer in any formulation, much less for a formulation suitable for use in a dry powder inhaler. Thus, none of the claims can be said to be obvious over Platz et al.

Applicants further point out that claims 17-30 (as amended), as well as new claims 33-60, claim (a) dry powder inhaler devices containing the compositions of the invention, and (b) methods of use thereof. The only rationale Platz et al. provide for including a surfactant in their polypeptide compositions is in order to aid in suspending the particles in the liquified propellant. A dry powder inhaler device does not

utilize liquified propellant. There is therefore no way to extract from Platz et al. a teaching that a surfactant should be included in a composition for use in a dry powder inhaler device.

In fact, Platz et al. specifically says that absorption enhancers are unnecessary:

> Moreover, [absorption of G-CSF] is accomplished without the necessity to resort to special measures such as the use of absorption enhancing agents or protein derivatives specifically designed to improve absorption. (Col. 2, lines 56-60)

Clearly, one of ordinary skill in the art relying on Platz et al. would have been dissuaded from making an inhalable polypeptide formulation that included an absorption enhancing agent. Rather than rendering such a formulation "obvious," Platz et al. actively teaches away from it. The rejection of the claims as obvious in view of Platz et al. should therefore be withdrawn.

B. Rubsamen in view of Platz et al.

The Examiner rejected claims 1-3, 5-11, 17, 18, 21, 22, 26, and 28 under 35 U.S.C. §103 as unpatentable over Rubsamen (U.S. Pat. No. 5,364,838) in view of Platz et al. This rejection is respectfully traversed on the grounds that, even in combination, the cited references do not teach or suggest the present invention.

As in the Platz et al. reference discussed above, Rubsamen discloses both (1) a polypeptide formulation intended for inhalation from a dry powder inhaler (insulin "provided as a dry powder by itself," col. 14, lines 56-58, and col. 15,

lines 54-64); and (2) a polypeptide formulation intended for inhalation from a powder MDI (col. 14, lines 45-56, and col. 15, lines 31-53). The first formulation explicitly includes only insulin, so by definition can include no absorption enhancers or other significant ingredients. The second formulation includes powdered insulin suspended in a propellant with an excipient "capable of allowing suspension of the insulin with the propellant" (col. 15, lines 48-50). Examples of such excipients are "oleic acid and related oils" (col. 15, lines 50-51).

Thus, Rubsamen comes no closer to the invention than does Platz et al. Neither reference suggests use of an ingredient that could be deemed an absorption enhancer that is a non-waxy solid at room temperature, as required by the present claims. Neither reference suggests inclusion of any kind of absorption enhancer (or even a surfactant such as oleic acid) in a formulation suitable for use in a dry powder inhaler, as required by the present claims. Certainly, neither reference suggests that it might be desirable to make a dry powder inhaler device containing such a composition. In fact, both references actively teach away from the invention.

Platz et al.'s teaching that absorption enhancers are unnecessary was discussed above. Rubsamen goes even further, and says that they not only are <u>unnecessary</u>, but furthermore <u>should be avoided</u>. Rubsamen's own invention "endeavors to overcome the problems of the prior art by <u>eliminating</u> the need for permeation enhancers" (col. 2, lines 57-59; emphasis added). Rubsamen points out that insulin formulations for nasal administration

which include certain "penetration enhancers" (i.e., absorption enhancers) have been demonstrated to cause nasal mucosal irritation (col. 1, lines 43-62), which would only be exacerbated by the continuous treatment necessary for chronic diabetes. This has prevented commercialization of such formulations (col. 1, lines 62-68). Furthermore, according to Rubsamen, any advantage that penetration enhancers may have in increasing absorption in the nose would not apply when the target tissue is the lung:

> Because the surface area of membranes available to absorb insulin is much greater in the lung than in the nose, no membrane penetration enhancers are required for delivery of insulin to the lungs by inhalation. Col. 2, lines 7-10.

By arguing that penetration enhancers for use in pulmonary formulations are not only unnecessary but in fact should be avoided, Rubsamen unequivocally teaches away from Applicants' invention. He thus is in full agreement with Platz et al.'s stated opinion that absorption enhancers are unnecessary. In view of these combined teachings and the amendments to the claims, Applicants request that the rejection for obviousness over Rubsamen and Platz et al. be withdrawn.

C. Rubsamen in view of Clark et al., Edman et al., and Mishima et al.

The Examiner rejected claims 1, 2, 6-18, 21, 22, and 28-32 under 35 U.S.C. §103 as unpatentable over Rubsamen in view of Clark et al. (U.S. Pat. No. 5,341,800) and further in view of Edman et al. (Advanced Drug Delivery Reviews 8:165-177, 1992) and

Mishima et al. (J. Pharmacol.-Dyn. 10:624-631, 1987). This rejection is traversed on the grounds that the cited art, even in combination, fails to teach or suggest the claimed invention.

Edman et al. and Mishima et al. were cited for their disclosures of various absorption enhancers used in formulations for nasal administration. They do not suggest use of these enhancers in any other kind of formulation. Rubsamen, as discussed above, explicitly teaches that

(a) absorption enhancers used to improve absorption in the nose have problems that have prevented their being commercialized, and

(b) use of such absorption enhancers is unnecessary and is to be avoided in formulations for pulmonary administration.

One of ordinary skill reading Rubsamen would find no motivation whatsoever to use the absorption enhancers of Edman et al. and Mishima et al. in the formulations of Rubsamen, and in fact would be actively discouraged from doing so. Clark et al. is cited solely for its general teachings about inhalers, and says nothing about absorption enhancers.

For the reasons stated above, the combination of the cited references fails to teach or suggest the presently claimed invention. In fact, Applicants submit that for any *prima facie* rejection of the present claims to stand, it would need to provide a motivation to make the claimed invention that is strong enough to overcome the bias against the use of absorption enhancers plainly expressed in both Platz et al. and especially

Rubsamen. Withdrawal of this and the other rejections under §103 is therefore requested.

CONCLUSION

It is submitted that all pending claims are in condition for allowance, and such action is respectfully requested. Submitted herewith is a check for $616.00 for the excess claims fee necessitated by the above amendment. Please apply any additional charges, or any credits, to Deposit Account No. 06-1050.

Respectfully submitted,

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